Associations of Ambulatory Blood Pressure With Urinary Caffeine and Caffeine Metabolite Excretions

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Abstract—Intake of caffeinated beverages might be associated with reduced cardiovascular mortality possibly via the lowering of blood pressure. We estimated the association of ambulatory blood pressure with urinary caffeine and caffeine metabolites in a population-based sample. Families were randomly selected from the general population of Swiss cities. Ambulatory blood pressure monitoring was conducted using validated devices. Urinary caffeine, paraxanthine, theophylline, and theobromine excretions were measured in 24 hours urine using ultrahigh performance liquid chromatography tandem mass spectrometry. We used mixed models to explore the associations of urinary excretions with blood pressure although adjusting for major confounders. The 836 participants (48.9% men) included in this analysis had mean age of 47.8 and mean 24-hour systolic and diastolic blood pressure of 120.1 and 78.0 mm Hg. For each doubling of caffeine excretion, 24-hour and night-time systolic blood pressure decreased by 0.642 and 1.107 mm Hg (both P values <0.040). Similar inverse associations were observed for paraxanthine and theophylline. Adjusted night-time systolic blood pressure in the first (lowest), second, third, and fourth (highest) quartile of paraxanthine urinary excretions were 110.3, 107.3, 107.3, and 105.1 mm Hg, respectively (P trend <0.05). No associations of urinary excretions with diastolic blood pressure were generally found, and theobromine excretion was not associated with blood pressure. Anti-hypertensive therapy, diabetes mellitus, and alcohol consumption modify the association of caffeine urinary excretion with systolic blood pressure. Ambulatory systolic blood pressure was inversely associated with urinary excretions of caffeine and other caffeine metabolites. Our results are compatible with a potential protective effect of caffeine on blood pressure. (***Hypertension*****. 2015;65:691-696. DOI: 10.1161/HYPERTENSIONAHA.114.04512.)** ● **Online Data Supplement**

Key Words: ambulatory blood pressure ■ caffeine ■ paraxanthine ■ population ■ theophylline

Hypertension is a major risk factor for cardiovascular disease and results from a complex interplay between genetic and environmental factors.[1] Intake of caffeinated beverages might be associated with lower cardiovascular mortality.[2] Caffeine, >70% of which is provided by coffee consumption,[3] is metabolized by the liver CYP1A2 enzyme into paraxanthine (≈80%), theobromine (≈12%), and theophylline (≈4%). Caffeine and caffeine metabolites are methylxanthines: a family of nonspecific adenosine receptor antagonist with several properties, including diuretic and natriuretic properties.[4,5] The urinary excretion of caffeine and caffeine metabolites is a valid measure of caffeine intake.[6]

The relation of blood pressure (BP) with caffeine and caffeine metabolites is of major interest, given their widespread consumption in foods and beverages (eg, coffee, tea, cola drinks, chocolate products) and the public health burden of high BP. Studies on the effect of acute consumption of caffeine at dietary levels on BP produced inconsistent results,[7] with a recent study restricted to nonsmokers showing a decrease in systolic BP (SBP).[8] In a cross-sectional study, high reported caffeine intake was associated with a lower prevalence of hypertension only in nonsmokers.[9]

To date, studies on the association of caffeine and BP have been limited by the use of reported caffeine intake instead of

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measured caffeine and caffeine metabolites and the use of office BP instead of ambulatory BP measurement (ABPM).[10] Recognizing this, we aimed to analyze the associations between ambulatory BP with urinary caffeine and caffeine metabolites excretions in the general adult population with the hypothesis that caffeine and metabolites excretions are inversely associated with BP.

Methods

SKIPOGH (Swiss Kidney Project on Genes in Hypertension) is a family and population-based cross-sectional study that examines the genetic determinants of BP. SKIPOGH is nested within the larger family-based international EPOGH study (European Project on Genes in Hypertension). SKIPOGH uses the same methods as that implemented and validated in the EPOGH study.[11] SKIPOGH has been described elsewhere.[12,13] Briefly, SKIPOGH is a multicenter study with participants being recruited in the cantons of Bern and Geneva and the city of Lausanne. Recruitment began in December 2009 and ended in April 2012 in Lausanne, in October 2012 in Geneva, and in April 2013 in Bern. Index cases were randomly selected from the population-based CoLaus study[14] in Lausanne and from the population-based Bus Santé study in Geneva.[15] In Bern, index participants were randomly selected using the cantonal phone directory. The SKIPOGH study was approved by the institutional ethical committees of the 3 participating university hospitals. All study participants provided written informed consent. The study population included 1128 participants coming from 273 nuclear families.

Participants filled in a detailed health questionnaire at home and attended the respective study centers in the morning where blood samples were collected after an overnight fast. Participants were also asked to collect a 24-hour urine sample, with separate day and night collections, for the measurement of urinary volume and electrolytes. Urinary sodium and potassium were measured using a Modular analyzer (Roche Diagnostics, Basel, Switzerland) in Lausanne and in Bern, and using the UniCel DxC 800 (Beckman Coulter, California, United States) in Geneva. Inter-center comparison based on 60 participants showed high Lin's correlation (0.99–1.00 for urinary sodium and 0.93–0.99 for urinary potassium). The CKD-EPI formula was used to calculate the estimated glomerular filtration rate.[16] Body weight and height were measured using precision electronic scales (Seca™, Hamburg, Germany). Body mass index was calculated as weight (kilogram) divided by height squared (meter). Diabetes mellitus was defined as a fasting glucose ≥7 mmol/L or presence of antidiabetic drug treatment (insulin or oral drugs). Participants were defined as smokers if currently smoking, non smokers otherwise.

Ambulatory Blood Pressure

Twenty-four hour ABPM was measured using validated Diasys Integra devices (Novacor, Rueil-Malmaison, France), which have fulfilled validation criteria of the British Hypertension Society and Association for the Advancement of Medical Instrumentation (AAMI) protocols.[17] Measurements were taken every 15 minutes during the day and every 30 minutes during the night (from 10 PM to 7 AM). Invalid BP values were defined as SBP >280 mm Hg or <60 mm Hg, diastolic BP (DBP) >200 mm Hg or <40 mm Hg, heart rate >200 bpm or <40 bpm, or DBP ≥SBP.[18] We used the awake and asleep periods as reported by participants to define day and night. Mean BP readings were then calculated using the valid 24-hour, daytime, and night-time measurements. The mean (min–max) number of 24-hour, daytime, and night-time measurements were 68.5 (18–100), 50.6 (3–82), and 17.9 (2–33).

Urinary Caffeine and Caffeine Metabolites

Quantification of caffeine, paraxanthine, theobromine, and theophylline in urine samples was performed by ultrahigh performance liquid chromatography (Waters ACQUITY UPLC I-Class) coupled to tandem mass spectrometry with electrospray ionization (Waters Xevo TQ-S). Sample preparation was performed by simple dilution. Limit of quantification was 10 ng/mL for caffeine, paraxanthine, and theophylline and 20 ng/mL for theobromine. The methods were fully validated according to the latest international guidelines using a stable isotope-labeled internal standard for each analyte. Expanded uncertainty (95% confidence level) calculated during routine use of the method was 8.2% for caffeine, 7.6% for paraxanthine, 7.8% for theobromine, and 8.1% for theophylline, respectively (Ansermot et al, manuscript in preparation, detailed method available on request).

Statistical Analysis

Continuous variables were described with mean or median and SD, SE, or interquartile range. Categorical variables were described with percentages. Twenty-four hours caffeine and paraxanthine urinary excretions were categorized into quartiles and associations with ABPM tested and illustrated. To satisfy normality assumptions, caffeine and caffeine metabolites were log-transformed. Association sizes were expressed as a 2-fold increase in the explanatory variables (without back transformation). Log base 2 was used so that the transformed beta coefficients can be interpreted as the effect on BP when the excretion of caffeine, respectively, caffeine metabolites, is doubled. We used mixed linear models to explore the associations of caffeine and caffeine metabolites levels with ambulatory SBP and DBP, although adjusting for major confounders, including sodium and potassium blood concentrations and 24-hour urinary excretions, and familial correlations. We used an independent covariance structure to accommodate familial dependencies. The estimations of the standard errors for the fixed effect parameters were model-based. Variables included in models as potential confounders were a priori considered, given their reported or potential influence on BP, methylxanthines, or both. The following variables were included in the models as potential confounders: age, sex, body mass index, oral contraceptive use, diabetes mellitus, current alcohol use and smoking, CKD-EPI estimated glomerular filtration rate, antihypertensive therapy (based on participants' self-reports list of drugs), blood Na^+ and K^+, and Na^+ and K^+ excretion. Models were further adjusted for study center to take into account the potential clustering of caffeine excretion and BP measurements by center. Relationship between 24-hour, daytime, and night-time SBP with 24-hour urinary excretions of caffeine and paraxanthine in quartiles are presented. After verifying that the linearity of association failed to be rejected, linear trends by urinary excretion of caffeine (respectively, paraxanthine) in quartiles (coded from 1 to 4) were tested using multilevel mixed-effects linear regression and *P* values reported (*P* for linear trend across quartiles). We also assessed the association of 24-hour, daytime, and night-time urinary caffeine and metabolites separately with the corresponding 24-hour, daytime, and night-time SBP and DBP. The actual awake and asleep periods were used, as reported by participants, to define daytime and night-time. BP and urine were, respectively, monitored and collected during 24-hour. Daytime collection usually started between 6 AM and 10 AM and ended at reported bedtime. Night-time collection started at bedtime and ended after the first morning urine. Creatinine excretion per body weight (kg) and urine volume were entered as covariates in sensitivity analysis models to account for the quality of urine collections. Sensitivity analyses were conducted to explore the association of ABPM with urinary caffeine and its major metabolite, paraxanthine, by participants' characteristics. For these sensitivity analyses, medians of continuous variables were used to categorize participants (except for body mass index and estimated glomerular filtration rate for which the general cutoff of 25 kg/m^2 and 60 $mL/min/1.73\ m^2$ were used, respectively). Statistical interactions between participants'characteristics and urinary caffeine excretion were tested using Wald tests. Significant interaction product terms were then included in the adjusted models. Given the apparent increased association between caffeine urinary excretion and BP in adults with antihypertensive therapy in preliminary analysis, stratified analyses by antihypertensive therapy were performed. Statistical significances for association and interaction were set at *P* value <0.05. Only those individuals for whom all covariates of interest for the purpose of this study were available were included in the analysis. All analyses were conducted using Stata, version 12.0 (StataCorp LP, College Station, TX).

Results

Among the 4173 eligible subjects invited to participate in the SKIPOGH study, 1128 (27.1%) participated and 836/1128

(74%) were included in the analysis. The main reason for participants to be excluded from the analysis were missing data on night-time BP (N=233) or day time BP (N=166), no data on 24-hour Na^+, K^+, or caffeine urinary excretions (N=38). Participants not included differed from participants included by urinary methylxanthines excretions, urinary 24-hour sodium excretion, smoking status, and night-time BP. Among the participants included (Table 1), the overall mean (±SD) of age, 24-hour SBP, and DBP were 47.8 (±17.5), 120.1 (±13.9) mm Hg, and 78.0 (±8.6) mm Hg, respectively. Urinary excretions of caffeine, paraxanthine, theophylline, and theobromine were highly skewed with medians of 3140.3, 10 177.5, 935.0, and 11 134.6 μg/24-hour, respectively. Night-time methylxanthines excretions were lower than daytime excretions. Fifteen percent were on antihypertensive therapy.

Figure presents, respectively, adjusted relationship of 24-hour, daytime, and night-time SBP with caffeine and, respectively, paraxanthine quartiles urinary excretions. Adjusted night-time SBP in the first (lowest), second, third, and fourth (highest) quartile of caffeine urinary excretions were 110.2 (0.9), 107.5 (0.9), 106.0 (0.9), and 106.2 (0.9) mm Hg, respectively. Adjusted night-time SBP in the second, third, and fourth quartiles differed significantly from the first (reference) quartiles. Adjusted night-time SBP in the first (lowest), second, third, and fourth (highest) quartile of paraxanthine urinary excretions were 110.3 (0.9), 107.3 (0.9), 107.3 (0.9), and 105.1 (0.9) mm Hg, respectively. Adjusted night-time SBP in the second, third, and fourth quartiles differed significantly from the first (reference) quartiles.

Table 2 displays the adjusted associations of 24-hour, daytime, and night-time SBP and DBP with urinary caffeine and caffeine metabolite excretions, respectively. Log-transformed urinary caffeine excretions were associated inversely with 24-hour and night-time ambulatory SBP. 24-hour and night-time ambulatory SBP decreased by 0.642 (SE, 0.296) and 1.107 (0.315) mm Hg (both P values <0.040) for each doubling excretion of caffeine. Stronger inverse associations with night-time ambulatory SBP were observed for paraxanthine and theophylline. Night-time ambulatory SBP decreased by 1.376 (SE, 0.364) and 1.183 (0.363) mm Hg (both P values <0.020) for each doubling excretion of paraxanthine and theophylline, respectively. No associations of theobromine levels with 24-hour or night-time ambulatory SBP were observed.

No associations of 24-hour, daytime, or night-time diastolic BP with 24-hour urinary excretions of caffeine, paraxanthine, theophylline, or theobromine were generally found (Table 2).

Adjusted associations of 24-hour, daytime, and night-time SBP and DBP separately with daytime and night-time urinary caffeine and caffeine metabolite excretions are displayed in Table S1 in the online-only Data Supplement. These separate analyses showed that the associations of SBP with methylxanthines are generally driven by daytime methylxanthine excretions. In addition, DBP—especially 24-hour and daytime DBP—appeared to be positively associated with night-time excretions of caffeine, paraxanthine, and theophylline.

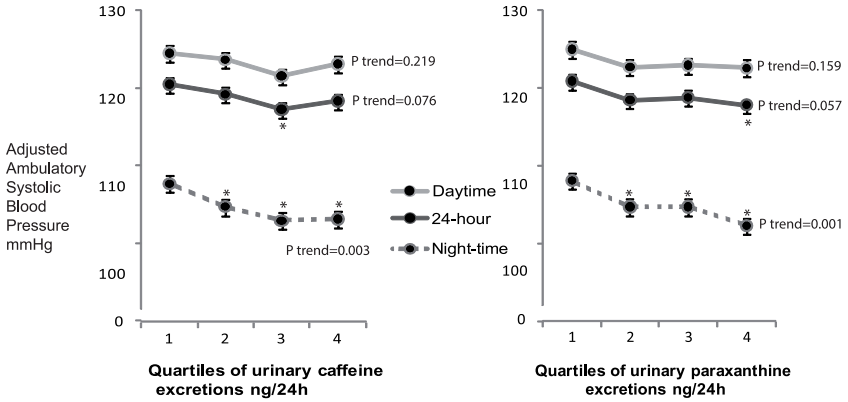
Table S2 in the online-only Data Supplement displays the adjusted associations of 24-hour, daytime, and night-time SBP and DBP with 24-hour urinary caffeine and caffeine metabolite excretions by antihypertensive therapy status. Inverse associations were stronger among participants with antihypertensive therapy than participants without antihypertensive therapy. Twenty-four hour, daytime, and night-time ambulatory SBP decreased by >3 mm Hg (all P values <0.005) for each doubling excretion of caffeine and caffeine metabolites (except theobromine). Inverse associations among participants without antihypertension therapy were found for night-time SBP.

Figures S1 in the online-only Data Supplement illustrates the adjusted associations of 24-hour, daytime, and night-time SBP with log-transformed urinary caffeine excretions for different participants' characteristics. The associations of SBP with urinary caffeine excretions were modified by antihypertensive

Table 1. Participants' Characteristics, SKIPOGH Study (N=836)

Charateristics	All (N=836, 100%)
Male sex, %	409 (48.9)
Smokers, %	188 (22.5)
Contraceptive use, % among women	347 (81.3)
Current alcohol use, %	532 (63.6)
Diabetes mellitus, %	38 (4.5)
Anti-hypertensive treatment, %	132 (15.8)
Age, mean (SD)	47.8 (17.5)
BMI, kg/m^2, mean (SD)	24.9 (4.3)
eGFR (CKD-EPI), mL/min/1.72 m^2 (SD)	96.4 (17.8)
Serum Na^+, mmol/L (SD)	140.4 (2.5)
Serum K^+, mmol/L (SD)	4.1 (0.3)
24-hour Na^+ urinary excretion (SD)	144.8 (62.7)
24-hour K^+ urinary excretion (SD)	64.5 (22.9)
Urinary methylxanthine excretions	
24-hour	
Caffeine median (IQR), μg/24 h	3140.3 (3967.8)
Paraxanthine median (IQR), μg/24 h	10 177.5 (10 966.8)
Theophylline median (IQR), μg/24 h	935.0 (999.2)
Theobromine median (IQR), μg/24 h	11 134.6 (12 498.3)
Day time	
Caffeine median (IQR), μg/d	2250.0 (3004.645)
Paraxanthine median (IQR), μg/d	6840.0 (7836.7)
Theophylline median (IQR), μg/d	600.7 (722.3)
Theobromine median (IQR), μg/d	6936.1 (8504.8)
Night-time	
Caffeine median (IQR), μg/night	617.2 (1033.6)
Paraxanthine median (IQR), μg/night	2925.9 (3598.1)
Theophylline median (IQR), μg/night	288.5 (334.4)
Theobromine median (IQR), μg/night	3273.2 (4414.9)
Ambulatory blood pressure (mm Hg)	
24-hour SBP (SD)	120.1 (13.9)
Day SBP (SD)	124.0 (14.7)
Night SBP (SD)	107.5 (14.4)
24-hour DBP (SD)	78.0 (8.6)
Day DBP (SD)	81.1 (9.6)
Night DBP (SD)	68.1 (8.3)

BMI indicates body mass index; DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; and SKIPOGH, Swiss Kidney Project on Genes in Hypertension.



*P value <0.05 compared to (lowest) quartile 1 (reference)

Figure. Adjusted associations (standard error) of 24-hour, daytime, night-time systolic blood pressure with quartiles of 24-hour urinary caffeine and paraxanthine excretions (N=836). adjusted for age, sex, body mass index, study center, contraceptive use, diabetes mellitus, current alcohol use, smoking, glomerular filtration rate (CKD-EPI), blood Na^+ and K^+, and Na^+ and K^+ excretion.

therapy, diabetes mellitus, and alcohol consumption. When these 3 interaction terms were all included in the adjusted models, all 3 interaction terms remained statistically significant with respect to night-time SBP (*P* values for interaction <0.05), whereas only antihypertensive and alcohol consumption modified the association of caffeine with both 24-hour and daytime SBP.

Discussion

In this population-based sample, we found that urinary caffeine, paraxanthine, and theophylline excretions were, in general, inversely associated with ambulatory SBP. To the best of our knowledge, no previous population-based study has looked at the association of measured urinary caffeine and caffeine metabolites on ambulatory BP. Our results are compatible with a protective effect of caffeine on high BP and hence on arterial hypertension.

Table 2. Adjusted Associations of Systolic and Diastolic Ambulatory Blood Pressure With 24-Hour Urinary Methylxanthines Excretions

	Systolic BP		Diastolic BP	
Methylxanthine	Beta, SE	*P* Value	Beta, SE	*P* Value
Caffeine*				
24 h	−0.642, 0.296	**0.030**	0.252, 0.182	0.166
Day	−0.505, 0.313	0.107	0.342, 0.202	0.091
Night	−1.107, 0.315	**<0.001**	−0.074, 0.183	0.686
Paraxanthine*				
24 h	−0.718, 0.343	**0.036**	0.353, 0.211	0.094
Day	−0.545, 0.362	0.132	0.442, 0.234	0.059
Night	−1.376, 0.364	**<0.001**	−0.039, 0.212	0.851
Theophylline*				
24 h	−0.633, 0.341	0.064	0.391, 0.209	0.062
Day	−0.458, 0.360	0.204	0.530, 0.232	**0.022**
Night	−1.183, 0.363	**0.001**	−0.032, 0.211	0.881
Theobromine*				
24 h	0.302, 0.338	0.372	0.237, 0.208	0.254
Day	0.325, 0.357	0.363	0.263, 0.230	0.254
Night	0.003, 0.361	0.993	−0.015, 0.209	0.942

Models are adjusted for age, sex, BMI, study center, contraceptive use, diabetes mellitus, current alcohol use and smoking, GFR (CKD-EPI), antihypertensive treatment, blood Na^+ and K^+, and Na+ and K^+ excretion. *P* values highlighted in bold are statistically significant (*P*<0.05). BMI indicates body mass index; BP, blood pressure; and GFR, glomerular filtration rate.

*Log-transformed.

Each doubling of the excretion of caffeine was associated with a 0.6 mm Hg lower 24-hour ambulatory SBP. Studies have shown that caffeine induces diuresis and natriuresis, and animal models have shown that intact adenosine receptors are required for the natriuretic action of caffeine.[19] Natriuresis associated with adenosine receptor blockade is thought to be caused by inhibition of proximal tubular reabsorption.[19] Further studies should ideally measure sodium proximal tubular reabsorption and determine its role in the caffeine–BP relation. Other methylxanthine-related mechanisms possibly involved include sympathomimetic effects, smooth muscle relaxation, and phosphodiesterase inhibition.[20,21]

We found no consistent association of 24-hour caffeine and caffeine metabolite excretions with DBP. Although the reason of the differential associations of caffeine and caffeine metabolites on SBP and DBP is not entirely clear, it is compatible with the hypothesis that methylxanthines influence BP via their natriuretic property. Previous studies with 24-hour urine collection reported that Na+ excretion predominantly affect SBP and generally not DBP.[22,23] An experimental study that explored the effects of acute caffeine on BP found no effect on DBP.[24] It is also possible that the adaptation of SBP and DBP to caffeine is different. DBP has been shown to adapt to repeated caffeine exposure, whereas SBP seems to consistently change in response to caffeine.[25,26] Interestingly, our additional analyses based on daytime and night-time excretions separately revealed that DBP—especially 24-hour and daytime DBP—was in fact positively associated with night-time excretions of caffeine, paraxanthine, and theophylline. Although the reasons of the observed differential associations between SBP and DBP, on the one hand, and between daytime and night-time methylxanthine excretions, on the other hand, remained speculative, it may explain, in part, the inconsistencies reported from previous studies that explored the association of caffeine with BP or hypertension. Inverse associations of 24-hour caffeine and caffeine metabolite excretions with SBP were strong during night-time. This could be explained, in part, by the fact that night-time BP is less influenced by environmental factors than daytime (and therefore 24-hour) BP, a

phenomenon previously reported in studies investigating the genetics of hypertension.[27] It is also possible that the inverse association during daytime is blunted by an acute pressure effect of caffeine intake during the morning. The stronger associations of night-time BP than daytime BP with caffeine is of importance, given the increasing evidence that night-time BP provides the greatest information regarding cariovascular risk.[28]

Similar results were observed for paraxanthine and theophylline. In fact, among all caffeine and caffeine metabolites, strong inverse association of paraxanthine with SBP was found. This is in line with the fact that paraxanthine is slightly more potent than caffeine in antagonising the effects of adenosine.[29]

Although theobromine has also been shown to increase natriuresis and to present similar properties than other methylxanthines,[21] we found no significant association of theobromine with BP. Theobromine has one fifth the stimulant effect of caffeine, and acute theobromine and caffeine intake have previously been shown to exert opposite results on BP among 24 healthy female volunteers.[30]

Interaction analysis suggested that antihypertensive therapy, diabetes mellitus, and alcohol consumption modify the association of caffeine urinary excretion with ambulatory SBP. It is possible that the potential diuretic effect of methylxanthines provides a synergistic effect to antihypertensive drugs. Of note, among participants with antihypertensive therapy, daytime SBP was also inversely associated with caffeine urinary excretions. Previous systematic reviews and meta-analysis on the effect of caffeinated beverages on BP have not stratified their analysis by diabetes mellitus status, and we are not aware of previous studies showing a differential association of caffeine with BP among individuals with and without type 2 diabetes mellitus.[31] The particularly strong associations in patients with antihypertensive therapy or diabetes mellitus deserve to be further explored. The stronger inverse association observed in participants who reported no alcohol consumption than participants who reported alcohol consumption is in line with previous evidence showing that long-term ethanol consumption masks the induction of CYP1A2 activity.[32] The significant interactions further suggest that the association of caffeine with BP is modified by multiple factors.

All together, our results are compatible with a protective effect of caffeine on BP. Although of major interest, definitive answer on the relation of BP with caffeine is currently lacking.[10] Also, cumulative evidence from clinical trials suggests that the acute and chronic effects of caffeine intake on BP may actually differ.[33]

Limitations and Strengths

The validity of caffeine and caffeine metabolites urinary excretion measurements depends on the quality of urine collection. The mean urinary volume corrected for 24 hour, and creatinine excretion corrected for body weight of the participants included in the analysis suggested that the quality of urine collection was satisfactory. Further adjustment for 24-hour urine volume and creatinine excretion did not change the associations (data not shown). Previous studies suggested that associations of caffeinated beverages (ie, coffee intake) with cardiovascular outcomes (ie, myocardial infarction) or risk factors (ie, hypertension) were modified by *CYP1A2* genotype.[9,34,35] Genetic information was not available in the present analysis. Although we considered major factors, the biological half-life of caffeine is highly variable among individuals (2–10 hours)[36] and is influenced by several genetic and nongenetic determinants (eg, liver function) that we could not account for.

The cross-sectional nature of our study limits causal inference. Similarly, we cannot exclude reverse causality. Yet, participants with antihypertensive therapy tended to have a greater urinary caffeine excretion than participants without antihypertensive therapy (3530.5 versus 3002.4 μg/24 h; *P* value 0.058). Finally, we performed multiple comparisons, and concern about false-positive associations could be raised. Many comparisons were, however, correlated or subgroup analysis (and thus need not be corrected) and all night-time BP-related associations would remain significant using a conservative approach, such as the Bonferroni correction.[37]

Strengths of our study include its population-based nature, the large sample size, the availability of ABPM, and the use of a standardized protocol across 3 study centers. Studies have shown that ambulatory BP is superior to office BP in predicting future cardiovascular events and target organ damage.[38] A large number of compounds other than caffeine are present in coffee, which limits the interpretation of many previous studies that assessed the role of caffeine on BP based on self-reported coffee intake. In addition, the caffeine content of coffee is highly variable.[39] To better disentangle the role of caffeine per se on BP, we directly measured caffeine and its main metabolites.

Perspectives

Ambulatory SBP was inversely associated with urinary caffeine and caffeine metabolites, paraxanthine and theophylline, in adults from the general population. Given the ubiquitous nature of caffeinated beverages and foods in the population, our results may have important public health effect.

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Disclosures

None.

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Novelty and Significance

What Is New?

- No previous study has ever addressed in a population-based study whether caffeine urinary excretion is associated with ambulatory blood pressure.

What Is Relevant?

- In our study, ambulatory systolic blood pressure was inversely associated with urinary excretions of caffeine and other caffeine metabolites.

Summary

Results from this population-based study with 24-hour caffeine urinary excretion and ambulatory blood pressure are compatible with a protective effect of caffeine on blood pressure.

ONLINE SUPPLEMENT

ASSOCIATIONS OF AMBULATORY BLOOD PRESSURE WITH URINARY CAFFEINE AND CAFFEINE METABOLITE EXCRETIONS

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Table S1. Adjusted associations of systolic and diastolic ambulatory blood pressure with day and night-time urinary methylxanthines excretions

	Daytime urinary methylxanthines excretions						Night-time urinary methylxanthines excretions					
	Systolic			Diastolic			Systolic			Diastolic		
Methylxanthine		Beta, SE	P value		Beta, SE	P value		Beta, SE	P value		Beta, SE	P value
Caffeine*	**SBP 24h**	-0.718, 0.280	**0.010**	**DBP 24h**	0.172, 0.172	0.319	**SBP 24h**	0.028, 0.252	0.911	**DBP 24h**	0.373, 0.154	**0.016**
	SBP day	-0.547, 0.313	0.065	**DBP day**	0.281, 0.191	0.142	**SBP day**	0.063, 0.266	0.814	**DBP day**	0.408, 0.171	**0.017**
	SBP night	-1.323, 0.315	**<0.001**	**DBP night**	-0.246, 0.173	0.155	**SBP night**	-0.048, 0.269	0.858	**DBP night**	0.308, 0.155	**0.048**
Paraxanthine*	**SBP 24h**	-0.748, 0.320	**0.019**	**DBP 24h**	0.318, 0.197	0.106	**SBP 24h**	-0.235, 0.304	0.439	**DBP 24h**	0.360, 0.186	0.053
	SBP day	-0.568, 0.338	0.093	**DBP day**	0.414, 0.218	0.058	**SBP day**	-0.125, 0.321	0.696	**DBP day**	0.415, 0.207	**0.044**
	SBP night	-1.509, 0.339	**<0.001**	**DBP night**	-0.159, 0.198	0.422	**SBP night**	-0.505, 0.324	0.119	**DBP night**	0.242, 0.187	0.196
Theophylline*	**SBP 24h**	-0.706, 0.321	**0.028**	**DBP 24h**	0.341, 0.198	0.085	**SBP 24h**	-0.268, 0.314	0.393	**DBP 24h**	0.381, 0.192	**0.048**
	SBP day	-0.521, 0.340	0.125	**DBP day**	0.485, 0.219	**0.027**	**SBP day**	-0.141, 0.331	0.671	**DBP day**	0.482, 0.213	**0.024**
	SBP night	-1.378, 0.341	**<0.001**	**DBP night**	-0.169, 0.199	0.394	**SBP night**	-0.523, 0.334	0.118	**DBP night**	0.199, 0.194	0.304
Theobromine*	**SBP 24h**	0.121, 0.325	0.710	**DBP 24h**	0.212, 0.200	0.287	**SBP 24h**	-0.389, 0.289	0.179	**DBP 24h**	0.166, 0.178	0.350
	SBP day	0.144, 0.343	0.675	**DBP day**	0.237, 0.221	0.284	**SBP day**	-0.383, 0.305	0.209	**DBP day**	0.177, 0.197	0.369
	SBP night	-0.237, 0.347	0.495	**DBP night**	-0.084, 0.201	0.674	**SBP night**	0.342, 0.309	0.268	**DBP night**	0.113, 0.179	0.527

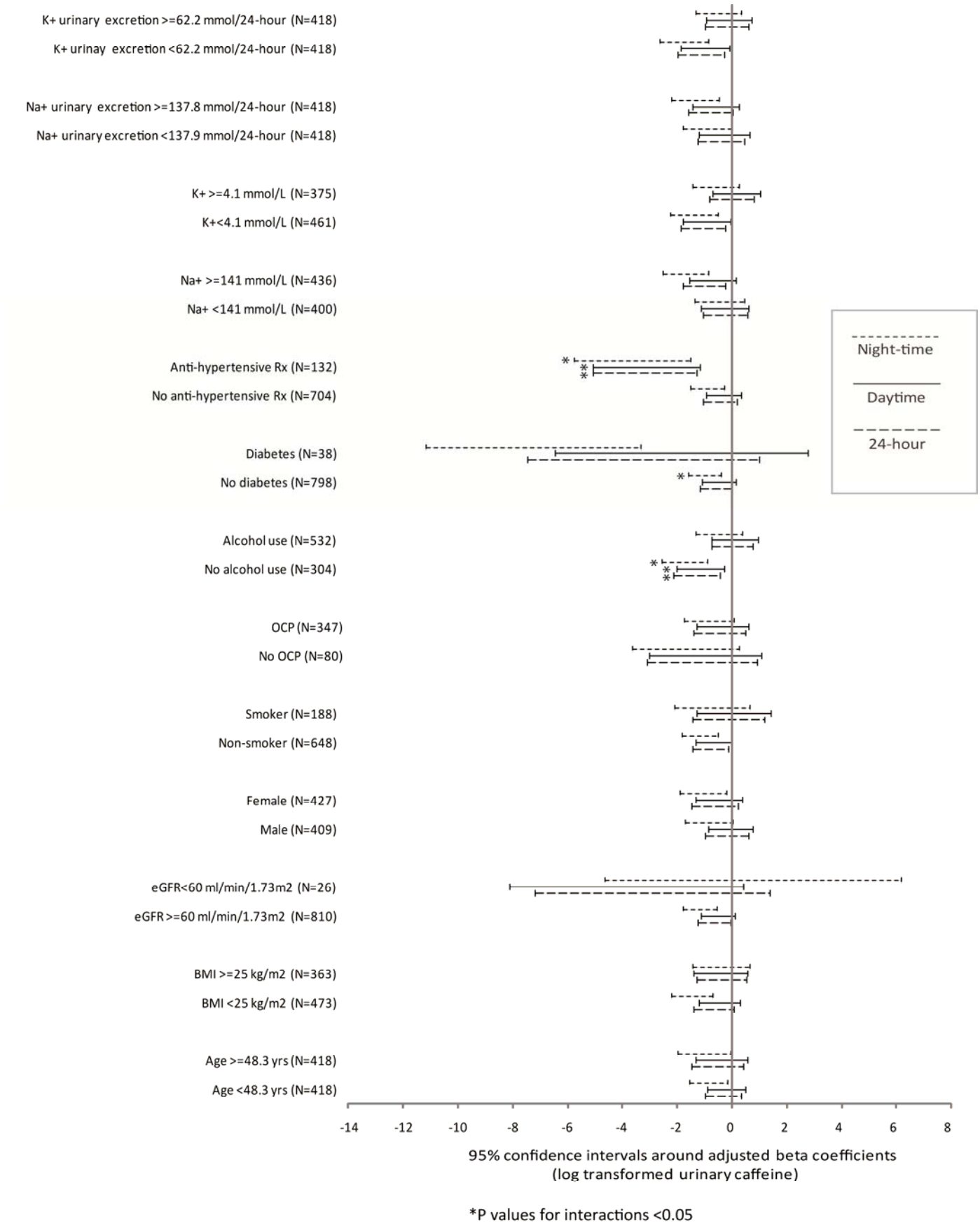
Models are adjusted for age, sex, BMI, study center, contraceptive use, diabetes, current alcohol use and smoking, GFR (CKD-EPI), anti-hypertensive treatment, blood Na^+ and K^+, and Na+ and K^+ excretion. *log-transformed

Table S2. Adjusted associations of systolic (SBP) and diastolic (DBP) blood pressure with 24-hour urinary methylanthines excretions

	NOT on anti-hypertensive therapy (N=704, 84.2%)						On anti-hypertensive therapy (N=132, 15.8%)					
	Systolic			Diastolic			Systolic			Diastolic		
Methylxanthine		Beta, SE	P value		Beta, SE	P value		Beta, SE	P value		Beta, SE	P value
Caffeine*	**SBP 24h**	-0.451, 0.311	0.147	**DBP 24h**	0.212, 0.186	0.255	**SBP 24h**	-3.192, 0.960	**0.001**	**DBP 24h**	-0.408, 0.626	0.515
	SBP day	-0.312, 0.330	0.344	**DBP day**	0.280, 0.206	0.174	**SBP day**	-3.088, 0.994	**0.002**	**DBP day**	-0.186, 0.707	0.793
	SBP night	-0.901, 0.325	**0.006**	**DBP night**	-0.064, 0.194	0.741	**SBP night**	-3.616, 1.091	**0.001**	**DBP night**	-1.093, 0.542	**0.044**
Paraxanthine*	**SBP 24h**	-0.533, 0.361	0.140	**DBP 24h**	0.314, 0.216	0.145	**SBP 24h**	-3.235, 1.090	**0.003**	**DBP 24h**	-0.448, 0.706	0.526
	SBP day	-0.347, 0.382	0.365	**DBP day**	0.414, 0.239	0.083	**SBP day**	-3.186, 1.127	**0.005**	**DBP day**	-0.501, 0.796	0.529
	SBP night	-1.209, 0.377	**0.001**	**DBP night**	-0.092, 0.224	0.681	**SBP night**	-3.558, 1.242	**0.004**	**DBP night**	-0.565, 0.617	0.360
Theophylline*	**SBP 24h**	-0.374, 0.362	0.303	**DBP 24h**	0.338, 0.216	0.119	**SBP 24h**	-3.481, 1.020	**0.001**	**DBP 24h**	-0.342, 0.667	0.608
	SBP day	-0.186, 0.384	0.628	**DBP day**	0.476, 0.239	**0.047**	**SBP day**	-3.415, 1.056	**0.001**	**DBP day**	-0.228, 0.753	0.762
	SBP night	-0.928, 0.379	**0.014**	**DBP night**	-0.069, 0.225	0.759	**SBP night**	-3.798, 1.163	**0.001**	**DBP night**	-0.839, 0.581	0.149
Theobromine*	**SBP 24h**	0.474, 0.359	0.187	**DBP 24h**	0.261, 0.214	0.224	**SBP 24h**	-1.021, 1.024	0.319	**DBP 24h**	0.320, 0.644	0.619
	SBP day	0.497, 0.380	0.191	**DBP day**	0.297, 0.238	0.211	**SBP day**	-0.995, 1.056	0.346	**DBP day**	-0.334, 0.726	0.646
	SBP night	0.215, 0.377	0.568	**DBP night**	0.014, 0.223	0.949	**SBP night**	-1.527, 1.160	0.188	**DBP night**	-0.656, 0.562	0.244

Models are adjusted for age, sex, BMI, study center, contraceptive use, diabetes, current alcohol use and smoking, GFR (CKD-EPI), blood Na^+ and K^+, and Na+ and K^+ excretion. *log-transformed

Figure S1.



*P values for interactions <0.05

Figure S1 Adjusted associations of 24-hour, daytime, and night-time systolic blood pressure with log transformed urinary 24-hour caffeine excretions, by participants' characteristics (N=836)

Footnote: adjusted for age, sex, BMI, study center, contraceptive use, diabetes, current alcohol use, smoking, GFR (CKD-EPI), blood Na^+ and K^+, and Na^+ and K^+ excretion.

Associations of Ambulatory Blood Pressure With Urinary Caffeine and Caffeine Metabolite Excretions

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